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REMARKS

I. Status Summary

Claims 1-19 are pending in the present application. Election by applicants of Group I, claims 1-17 has been acknowledged by the U.S. Patent and Trademark Office (hereinafter "the Patent Office") and claims 1-3, 5-10 and 12-17 currently examined. Claims 18-19 have been withdrawn from prosecution at this time and claims 4 and 11 have been canceled. Claims 1, 5-6, 8-9, and 13-16 are currently amended.

Claims 1, 2, 9 and 16-17 presently stand rejected under 35 USC § 103(a) as allegedly being obvious over U.S. Patent No. 5,252,466 to Cronan (hereinafter "Cronan") in view of U.S. Patent No. 5,283,173 to Fields *et al.* (hereinafter "Fields *et al.*"). Claims 1, 2, 5-9 and 12-16 presently stand rejected under 35 USC § 103(a) as allegedly being obvious over Cronan in view of Fields *et al.* and further in view of the journal article to Rigaut *et al.* (*Nature Biotech.*, **17**: 1030-1032, 1999; hereinafter "Rigaut *et al.*"). Claims 1-3, 5-10 and 12-17 presently stand rejected under 35 USC § 103(a) as allegedly being obvious over Cronan in view of Fields *et al.*, further in view of Rigaut *et al.*, and further in view of U.S. Patent No. 6,114,111 to Luo *et al.* (hereinafter "Luo *et al.*").

II. Response to the Rejections Under 35 U.S.C. § 103

II.A. Cronan in view of Fields et al.

Claims 1, 2, 9 and 16-17 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Cronan in view of Fields *et al.*

Applicants respectfully submit that one of ordinary skill in the art would not have had a motivation to combine Cronan with the teachings of Fields *et al.* and, in any case, even if the references were to be combined the combination would fail to teach or suggest every element of claims 1, 2, 9 and 16-17. Cronan does not teach "binding partners" to a protein of interest as the phrase "binding partners" is used by

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Applicants and, accordingly, one of ordinary skill in the art could not have had a motivation to combine Cronan and Fields *et al.* on such a basis. The Examiner seems to be suggesting that Cronan does teach obtaining such "binding partners", and the reference is only lacking in teaching the identification of the binding partners. (See Official Action, page 4, first full paragraph). To the contrary, the binding factors in Cronan are *provided* as part of the disclosed procedure for purifying the protein of interest and, thus, there is no need to "identify" these binding partners.

It is respectfully submitted that there is a misapprehension of the meaning of "binding factors" as used in the Cronan reference versus use of the phrase in Applicants' disclosed subject matter. Cronan is using "binding partners" to mean the binding partner for the molecule which is attached by post-translational modification to the engineered site. This is why the Cronan reference specifically states: "*providing* a binding partner that binds to the fusion protein *only after it has been modified*". (*See*, e.g., the Abstract at page 1; the Summary at column 5, line 68 (emphasis added)). Cronan is directed to protein purification by *providing a known* binding partner to the tag as part of the purification procedure. In contrast, Applicants are using "binding partners" to mean molecules that bind to the protein of interest at areas other than the post-translational modification. The binding partners disclosed by Applicants are not provided, and are not part of the procedure for separating the protein of interest from the cellular extract as is the case in Cronan.

In the claims, it does not matter whether the "binding partner" binds before or after the occurrence of the post-translational modification. Applicants' binding partner is not binding to the molecule added by post-translational modification. For example, each of amended independent claims 1, 9 and 16 is directed to obtaining or screening for "binding partners", and each of these claims includes a step for contacting the tagged fusion protein with an affinity purification reagent while the tagged fusion protein is present in the cellular extract, and each claim contains a step for identifying binding partners that bind to the protein of interest. Applicants describe binding of both an affinity purification reagent *and* binding partners to the protein of interest. The binding partners described in Cronan at best relate to the

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"affinity purification reagent", rather than the "binding partners" in the claims. Claims 1 and 9 are currently amended at step (b) to further point out and clarify the difference between the binding partners to be identified and the affinity purification reagent used in separating the fusion protein from the cellular extract. Support for the amendment to claims 1 and 9 can be found throughout the specification as filed, including, in particular, the Summary at page 4, lines 1-8; the Detailed Description at page 9, lines 5-15 and 24-31; page 14, lines 22-24; page 17, lines 12-20; page 18, lines 16-19; page 22, lines 5-21; and pages 24-25. No new matter has been added.

The phrase "binding partner" is used by both Cronan and Applicants. However, the phrase is used differently in each case. This difference in meaning would have been readily apparent to one of ordinary skill in the art at the time the instant application was filed. Accordingly, the skilled artisan would not have had a motivation to combine Cronan with Fields *et al.* There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Prior art references must be considered in their entirety, i.e., as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984).

A skilled artisan would not have had a motivation based on use of the phrase "binding factors" in Cronan to combine the reference with the teachings of Fields *et al*. While Fields *et al.* is directed to the identification of protein-protein interactions within a cell, Cronan only teaches separation of a protein from a cellular extract by provision of a known binding partner/affinity purification reagent. Since Cronan does not teach or suggest identifying non-affinity purification reagent binding partners to the protein of interest, one of ordinary skill in the art desiring to identify such binding partners would not be motivated to turn to Cronan to look for desired components, as Cronan does not teach or suggest a key component of the endeavor, that is, identifying binding partners of a protein of interest. As such, Applicants respectfully

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submit there is no suggestion or motivation to combine the teachings of Cronan and Fields *et al.*

Furthermore, even if Cronan were combined with Fields *et al.*, every element of claims 1, 2, 9 and 16-17 could not be present without destroying operability. To establish *prima facie* obviousness, each and every claim limitation must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Fields *et al.* use a yeast two-hybrid system to identify the interaction between two proteins of interest. In Fields *et al.*, the protein-protein interaction is identified by reconstitution of transcriptional activation of a reporter gene. Once the Cronan and Fields *et al.* methods are combined, it is not possible to perform every step of independent Claims 1, 9 and 16. For example, part (d) of claims 1, 9 and 16 describes separating the tagged fusion protein-affinity purification reagent complex from the cell extract, and part (e) recites identifying any binding partners of the protein of interest. However, in the Fields *et al.* method, separation of one or both of the proteins of interest from the cell extract would make detection of the binding partner impossible, because the transcriptional activation reporter system requires the presence of the cellular extract to function. When the methods of Cronan and Fields *et al.* are combined, every element of the claims cannot be present without destroying operability. Therefore, the combination of Cronan and Fields *et al.* fails to teach or suggest every element of independent claims 1, 9 and 16. Accordingly, the claims cannot be rendered obvious by the proposed combination.

Applicants respectfully submit that because there is no motivation to combine the teachings of Cronan and Fields *et al.*, and the proposed combination would result in the inoperability of independent claims 1, 9 and 16, the cited combination does not support the instant rejection of these claims. Claims 2 and 17 depend from independent claims 1 and 16, respectively and, therefore, support for the rejection of these claims is similarly lacking. Hence, Applicants respectfully submit that a *prima facie* case of obviousness has not been established, and Applicants respectfully request the instant rejection of claims 1, 2, 9 and 16-17 under 35 U.S.C. § 103(a) be withdrawn. Allowance of these claims is also respectfully requested.

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II.B. Cronan in view of Fields et al., in further view of Rigaut et al.

Claims 1, 2, 5-9 and 12-16 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Cronan in view of Fields *et al.*, and in further view of Rigaut *et al.*

Applicants respectfully submit that one of ordinary skill in the art would not have had any motivation to combine Cronan with the teachings of either Fields *et al.* or Rigaut *et al.* and, in any case, even if the references were to be combined, the combination would fail to disclose every element of claims 1, 2, 5-9 and 12-16. As described above, one of ordinary skill in the art would not have been motivated to combine the Cronan and Fields *et al.* references, as there is no suggestion or teaching in Cronan to identify non-affinity reagent-type binding partners to a protein of interest. Furthermore, the proposed combination renders impossible the performance of every element of independent claims 1, 9 and 16 without destroying operability. The addition of the Rigaut *et al.* reference fails to rectify this deficiency and, in any case, Rigaut *et al.* teaches away from combination with Cronan.

One of ordinary skill in the art would not have been motivated to combine Rigaut *et al.* with Cronan, as Rigaut *et al.* teaches away from Cronan. Furthermore, even if Rigaut *et al.* were combined as proposed, the resulting combination would still fail to teach or suggest every element of amended claims 1, 2, 5-9 and 12-16. Rigaut *et al.* teaches transforming a yeast cell with a fusion protein comprising a heterologous protein with two affinity tags (two IgG-binding units of protein A (ProtA) and a calmodulin binding peptide (CBP)) and a TEV cleavage site. Rigaut *et al.* designate the fusion cassette encoding the CBP, TEV cleavage site, and ProtA the tandem affinity purification (TAP) tag due to its consisting of two different affinity tags. Rigaut *et al.* describe a method for protein purification and protein complex characterization using the serial two high-affinity tag purification system. Rigaut *et al.* teaches away from Cronan by expressly stating and demonstrating the necessity of having the two-step serial affinity purification procedure. (*See* Rigaut *et al.* at page 1031, column 1).

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Independent claims 1, 9 and 16 presently recite a cell transformed to express a fusion protein having a single post-translational modification sequence resulting in a singly tagged fusion protein. Support for the claim amendments can be found throughout the specification and claims as filed and in particular at the Summary, page 4, lines 1-8; Figure 1; and Example 1, pages 19-26. No new matter has been added. Given the express requirement for using tandem two affinity tag purification in Rigaut *et al.*, one of ordinary skill in the art would not have had a reasonable expectation of success in combining Rigaut *et al.* with the method of Cronan, to obtain the single affinity reagent separation procedure as recited in independent claims 1, 9 and 16. Indeed, Rigaut *et al.* is believed to provide evidence that the success of the instantly claimed methods was contrary to the expectations of skilled artisans at the time of filing of the present U.S. patent application. Accordingly, one of ordinary skill in the art would not have expected success in the proposed combination, and consequently would not have been motivated to combine Cronan with Rigaut *et al.* in such manner.

Furthermore, even if Rigaut *et al.* were combined with Cronan and Fields *et al.*, every element of claims 1, 2, 5-9 and 12-16 would not be taught or suggested. To establish *prima facie* obviousness, each and every claim limitation must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). As described above, the Rigaut *et al.* reference teaches away from the claim limitations of a single post-translational modification sequence and a singly tagged fusion protein. Accordingly, the combination of Cronan, Fields *et al.* and Rigaut *et al.* fails to teach or suggest every element of the claims. Therefore, claims 1, 9 and 16 cannot be rendered obvious by the proposed combination.

Applicants respectfully submit that because a skilled artisan could not have expected success in combining Cronan and Fields *et al.* and the proposed combination of Cronan, Fields *et al.* and Rigaut *et al.* would, in any case, fail to teach or suggest every element of independent claims 1 and 9 and 16 as the claims would be rendered inoperable, the cited combination does not support the instant rejection of these claims. Claims 2, 5-8 and 12-15 depend from independent claims 1 and 9,

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and therefore support for the rejection of these claims is similarly lacking. Hence, Applicants respectfully submit that a *prima facie* case of obviousness has not been established, and Applicants respectfully request the instant rejection of claims 1, 2, 5-9 and 12-16 under 35 U.S.C. § 103(a) be withdrawn. Allowance of these claims is also respectfully requested.

II.C. Cronan in view of Fields et al., in view of Rigaut et al. and in view of Luo et al.

Claims 1-3, 5-10 and 12-17 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Cronan in view of Rigaut *et al.*, in further view of Fields *et al.*, and in further view of Luo *et al.*

Applicants respectfully submit that one of ordinary skill in the art would not have had any motivation to combine Cronan with the teachings of either Fields *et al.* or Rigaut *et al.* or Luo *et al.* and, in any case, even if the references were to be combined, the combination would fail to teach or suggest every element of claims 1-3, 5-10 and 12-17 and would render the methods inoperable. As described above, one of ordinary skill in the art would not have been motivated to combine Cronan with Fields *et al.* or Rigaut *et al.*, as there is no suggestion or teaching for the combination and, in any case, the combination would render impossible the performance of every element of independent claims 1, 9 and 16 without destroying operability. The addition of the Luo *et al.* reference fails to rectify this deficiency, and in a manner similar to the Fields *et al.* reference, would render the claims inoperable.

Similar to the case of Fields *et al.* described above, one of ordinary skill in the art would not have had a motivation based on use of the phrase "binding factors" in Cronan to combine the reference with the teachings of Luo *et al.* While Luo *et al.* is directed to the identification of protein-protein interactions within a cell, Cronan only teaches separation of a protein from a cellular extract by provision of a known binding partner/affinity purification reagent. Since Cronan does not teach or suggest identifying non-affinity purification reagent binding partners to the protein of interest, one of ordinary skill in the art desiring to identify such binding partners would not be

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motivated to turn to Cronan to look for desired components, as Cronan does not teach or suggest a key component of the endeavor, that is, identifying binding partners of a protein of interest. As such, applicants respectfully submit there is no suggestion or motivation to combine the teachings of Cronan and Luo *et al.*

Furthermore, even if Cronan were combined with Luo *et al.*, every element of claims 1-3, 5-10 and 12-17 could not be present without destroying operability. To establish *prima facie* obviousness, each and every claim limitation must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). In Luo *et al.*, protein-protein interactions are identified by reconstitution of transcriptional activation of a reporter gene. Once the Cronan and Luo *et al.* methods are combined, it is not possible to perform every step of independent Claims 1, 9 and 16. For example, part (d) of claims 1, 9 and 16 describes separating the singly tagged fusion protein-affinity purification reagent complex from the cell extract, and part (e) recites identifying any binding partners of the protein of interest. However, in the Luo *et al.* method, separation of one or both of the proteins of interest from the cell extract would make detection of the binding partner impossible, because the transcriptional activation reporter system requires the presence of the cellular extract to function. When the methods of Cronan and Luo *et al.* are combined, every element of the claims cannot be present without destroying operability. Therefore, the combination of Cronan and Luo *et al.* fails to teach or suggest every element of independent claims 1, 9 and 16. Accordingly, the claims cannot be rendered obvious by the proposed combination.

Applicants respectfully submit that because a skilled artisan would not have been motivated to combine Cronan and Luo *et al.* and the proposed combination of Cronan, Fields *et al.*, Rigaut *et al.* and Luo *et al.* would, in any case, render inoperable independent claims 1, 9 and 16, the cited combination does not support the instant rejection of these claims. Claims 2-3, 5-8, 10, 12-15 and 17 depend from independent claims 1, 9 and 16 and, therefore, support for the rejection of these claims is similarly lacking. Hence, Applicants respectfully submit that a *prima facie* case of obviousness has not been established, and Applicants respectfully request

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the instant rejection of claims 1-3, 5-10 and 12-17 under 35 U.S.C. § 103(a) be withdrawn. Allowance of these claims is also respectfully requested.

CONCLUSION

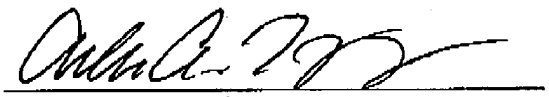
In light of the above amendments and remarks, it is respectfully submitted that the present application is now in proper condition for allowance, and an early notice to such effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

DEPOSIT ACCOUNT

Although it is believed that no fee is due, the Commissioner is hereby authorized to charge any fees associated with the filing of this Response, or credit any overpayment, to Deposit Account No. **50-0426**.

Respectfully submitted,
JENKINS, WILSON, TAYLOR & HUNT, P.A.

Date: January 24, 2008 By: 

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